ELECTRONIC LETTER

Hepatic lipase C-480T polymorphism modifies the effect of HDL cholesterol on the risk of acute myocardial infarction in men: a prospective population based study

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Previous studies have revealed an inverse association between high density lipoprotein cholesterol (HDL-C) levels and the risk of acute myocardial infarction (AMI).[1 2] HDL-C level is modulated by genetic factors as well as environmental factors such as obesity, smoking, and physical exercise. Hepatic lipase (HL) is a lipolytic enzyme in lipoprotein metabolism, functioning as a phospholipase, an acylglycerol hydrolase, and a ligand of cell surface glycosaminoglycans, hydrolysing triglyceride-rich lipoprotein particles.[3] Recently, it has been reported that HL is synthesised by macrophages.[4] The HL gene variation has a significant effect on the variability of HDL-C in the population.[5 6] The functional HL promoter C-480T transition, also referred to as (-514C/T), leads to three common genotypes: CC, CT, and TT. The C and T alleles are associated with high and low HL activity, respectively.[7–9] However, the common polymorphisms of HL (-480T), cholesterol ester transfer protein (CETP) (TaqIB), lipoprotein lipase (S447X), and lecithin cholesterol acyl transferase (S208T) contribute only about 2.5% to the variance of HDL-C in the population.[10] This suggests that the HL C-480T polymorphism and HDL-C levels are different factors, and studying their interaction is justified. One previous study has shown that there might be an interaction between CETP gene polymorphism and HDL-C on the risk of myocardial infarction.[11] This result raises the possibility that other polymorphisms associated with HDL-C—for example, HL gene polymorphism—might interact with HDL-C and thus modify the risk of AMI. In fact, an effect of the C-480T polymorphism on coronary artery disease (CAD) has been sought in several studies with both negative[7 12] and positive findings.[13–15] One possible reason for the mixed results may be the interaction between HL C-480T genotype and HDL levels on CAD, a hypothesis not studied previously. To address this question, and to prospectively examine the relationship between the C-480T polymorphism of the HL gene and subsequent occurrence of AMI, we conducted a population based study in a cohort of Finnish men of middle age and with no previous history of coronary disease. We also explored the interaction between C-480T polymorphism and HDL-C levels on the risk of developing AMI.

Key points

- Decreased high density lipoprotein cholesterol (HDL-C) level is a well known risk factor for acute myocardial infarction (AMI). Hepatic lipase (HL) promoter C-480T transition, affecting gene transcription and leading to genotypes CC, CT, and TT, has been shown to be associated with HL activity and HDL-C concentration. We examined the relationship between C-480T polymorphism and subsequent occurrence of AMI in a prospective population based cohort of 126 men who developed AMI during follow up and 260 matched controls.
- Men with CC genotype tend to have a higher risk for AMI compared with T allele carriers, after adjustment for age, body mass index, smoking, years of hypertension, diabetes, family history of coronary disease, total cholesterol, triglycerides, and total energy and fat intake. However, when HDL-C is added additionally as covariate in an otherwise similar model, this association disappears.
- Men with CC genotype and HDL-C concentration in the lowest or second lowest tertile were found to have a 4/1 and 3.3/1 risk of developing AMI, respectively, compared with men in the highest HDL-C tertile, after adjusting for risk factors. A similar effect was not found in men with the T allele.
- The HL C-480T polymorphism might affect AMI risk differently in men with different HDL-C levels; the atherogenicity of low concentrations of HDL-C may be modulated diversely by different C-480T genotypes as well.

MATERIALS AND METHODS

Study subjects

The study subjects were from the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD). The study protocol was approved by the Research Ethics Committee of the University of Kuopio. A total of 2682 men from Eastern Finland, aged 42, 48, 54, or 60, were examined from 1984 to 1989. A DNA sample was available for 1263 of the men. A subpopulation of 480 men, which consisted of 160 men who developed AMI between the years 1985 and 1997, and two matched controls for each of them, was selected for this study. The average follow up time was nine years. To ensure the comparability of the control subjects, they were drawn from the same cohort (KIHD) as the cases. The controls were matched according to age, smoking, dietary iron, dietary saturated fatty acids, dietary cholesterol, and hair mercury content. In addition, examination year and month and the place of residence were identical for each case and the corresponding control. Because of inadequate blood samples, 94 of the men were excluded, leaving 386 men (126 men with AMI and 260 controls) for the final analysis. All participants gave written informed consent.

Examination protocol

The KIHD examination protocol and measurements have been described previously.[1] Subjects arrived to give fasting

venous blood samples in the morning. They had been instructed to abstain from alcohol for the three preceding days, and from smoking and eating for 12 hours. Blood was drawn after 30 minutes of supine rest. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). The consumption of foods was assessed at the time of blood sampling, with instructions for food recording using household measures over four days. The instructions were given and the completed food records were checked by a nutritionist. The intake of nutrients and total energy intake were estimated by means of Nutrica software. The Nutrica databank uses mainly Finnish values for measuring nutrients. HL promoter C-480T genotype was determined by PCR and restriction enzyme *Nla*III digestion.[16]

Statistical analysis

Differences of risk factors between the cases and controls were tested for significance with Student's *t* test. To evaluate the relationship between HL genotypes and dependent variables, we used one way analysis of covariance (ANCOVA). Discontinuous variables, and the trend for the prevalence of genotypes according to HDL-C tertiles in the AMI and the control groups, were analysed using χ^2 tests. Logistic regression modelling was employed to examine associations between genotype and AMI, adjusted for age, BMI, smoking, years of hypertension, diabetes, family history of CAD, total cholesterol, triglycerides, and energy and fat intake. Finally, we further explored in a multivariate analysis the interaction between HL C-480T polymorphism and HDL-C tertiles on the risk of developing AMI. All statistical analyses were performed using SPSS version 11.5.

RESULTS

Table 1 shows the baseline characteristics for the AMI and the control groups. Age, smoking status, and total energy and fat intake did not differ significantly in the two groups, because they were matched for these factors. The AMI group, however, had significantly higher serum total cholesterol, LDL cholesterol, and apolipoprotein B, and lower HDL-C, than the control group. Diabetes and family history of CAD were more prevalent in the AMI group than in the control group.

Of the cases, 67 (53.2%) were CC homozygous, 47 (37.3%) were heterozygous, and 12 (9.5%) were TT homozygous. Of the controls, 124 (47.7%) had CC genotype, 108 (41.5%) had CT genotype, and 28 (10.8%) had TT genotype. Because the number of TT homozygous subjects in the AMI group was small, and there was no statistically significant difference between the T allele carrier groups in any background characteristics, the allele T carriers (CT, TT) were combined into one group which was compared with the group of CC homozygous participants.

In all subjects, the T allele carriers had higher total cholesterol ($p = 0.004$), apolipoprotein AI ($p = 0.028$), and HDL-C ($p = 0.09$) than men with CC genotype (table 2). In the AMI group, the T allele carriers tended to have higher HDL-C ($p = 0.093$) and apolipoprotein AI ($p = 0.079$) than men with CC genotype (table 2). In the control group, the T allele carriers had higher total cholesterol ($p = 0.009$) and apolipoprotein B ($p = 0.035$) than men with CC genotype (table 2).

Men with CC genotype tended to have a higher risk for AMI (relative risk, 1.5; 95% CI, 1.0 to 2.4; $p = 0.07$) as compared with T allele carriers after adjustment for age, BMI, smoking, years of hypertension, diabetes, family history of coronary disease, total cholesterol, triglycerides, and energy and fat intake. However, when HDL-C was added as covariate in an otherwise similar model, this association disappeared (table 3). Therefore, we further explored the interaction between C-480T polymorphism and HDL-C levels on the risk of developing AMI. For that purpose we divided the subjects into tertiles according to their serum HDL-C concentrations. The lowest tertile had HDL-C below 1.14 mmol/l, whereas the

Table 1 Baseline characteristics of subjects who developed AMI during follow up, and controls

Characteristic	AMI (n = 126)	Controls (n = 260)	p Value
Age	54.5 (3.8)	54.3 (4.6)	0.697
Body mass index (kg/m^2)	27.3 (3.7)	26.6 (3.1)	0.074
Proportion of smokers	36.5% (46)	29.6% (77)	0.200
Years of hypertension	3.1 (5.2)	3.0 (5.8)	0.793
Diabetes	12.7% (16)	5.0% (13)	0.012
Family history of coronary disease	57.1% (72)	45.4% (118)	0.039
Total fat intake (g, 4d mean)	112.5 (40.4)	118.6 (36.7)	0.142
Total energy intake (kJ, 4d mean)	10751 (3166)	11170 (2826)	0.190
Serum total cholesterol (mmol/l)	6.28 (1.25)	5.95 (1.02)	0.007
Serum LDL cholesterol (mmol/l)	4.39 (1.03)	4.05 (0.99)	0.002
Serum HDL cholesterol (mmol/l)	1.22 (0.27)	1.33 (0.29)	<0.001
Serum triglycerides (mmol/l)	1.40 (0.76)	1.37 (0.98)	0.251
Serum apolipoprotein B (g/l)	1.12 (0.22)	1.03 (0.22)	0.001
Serum apolipoprotein AI (g/l)	1.33 (0.26)	1.36 (0.24)	0.316

Data are mean (SD) or per cent (number of participants).
AMI, acute myocardial infarction; n, number.

Table 2 Baseline characteristics of subjects according to HL C-480T genotype and AMI status, during follow up

	HL C-480T genotype		
	CC	CT, TT	p Value
All subjects			
Number	191	195	
Serum total cholesterol (mmol/l)	5.89 (1.03)	6.22 (1.17)	0.004
Serum LDL cholesterol (mmol/l)	4.09 (1.00)	4.22 (1.03)	0.270
Serum HDL cholesterol (mmol/l)	1.28 (0.29)	1.31 (0.28)	0.090
Serum apolipoprotein B (g/l)	1.04 (0.23)	1.08 (0.22)	0.142
Serum apolipoprotein AI (g/l)	1.33 (0.23)	1.37 (0.26)	0.028
Serum triglycerides (mmol/l)	1.28 (0.69)	1.47 (1.08)	0.210
Subjects with AMI			
Number	67	59	
Serum total cholesterol (mmol/l)	6.10 (1.04)	6.48 (1.44)	0.106
Serum LDL cholesterol (mmol/l)	4.37 (0.98)	4.42 (1.09)	0.732
Serum HDL cholesterol (mmol/l)	1.19 (0.28)	1.26 (0.25)	0.093
Serum apolipoprotein B (g/l)	1.11 (0.22)	1.12 (0.23)	0.922
Serum apolipoprotein AI (g/l)	1.30 (0.24)	1.37 (0.28)	0.079
Serum triglycerides (mmol/l)	1.33 (0.62)	1.46 (0.90)	0.596
Control group			
Number	124	136	
Serum total cholesterol (mmol/l)	5.78 (1.00)	6.12 (1.02)	0.009
Serum LDL cholesterol (mmol/l)	3.94 (0.98)	4.14 (0.99)	0.125
Serum HDL cholesterol (mmol/l)	1.33 (0.29)	1.33 (0.29)	0.497
Serum apolipoprotein B (g/l)	1.00 (0.22)	1.07 (0.22)	0.035
Serum apolipoprotein AI (g/l)	1.34 (0.23)	1.37 (0.26)	0.179
Serum triglycerides (mmol/l)	1.25 (0.72)	1.47 (1.15)	0.272

Values are mean (SD). Significance based on ANCOVA. with age, body mass index, smoking, years of hypertension, diabetes, and family history of coronary disease as covariates.
AMI, acute myocardial infarction.

Table 3 Relative risk of acute myocardial infarction according to HL C-480T genotype status

	HL C-480T genotype		
Relative risk	CT, TT	CC	p Value
Number of participants	195	191	
Number of cases of AMI	59	67	
Number of controls	136	124	
RR	1.0	1.245 (0.813–1.907)	0.313
Age and smoking adjusted RR	1.0	1.289 (0.839–1.982)	0.247
Multivariate adjusted RR*	1.0	1.558 (0.986–2.459)	0.057
Multivariate adjusted RR†	1.0	1.531 (0.965–2.429)	0.070
Multivariate adjusted RR‡	1.0	1.405 (0.878–2.248)	0.156

AMI, acute myocardial infarction; RR, relative risk (95% confidence interval).
*Adjusted for age, body mass index, smoking, years of hypertension, diabetes, family history of coronary disease, and total cholesterol and triglycerides.
†Additionally adjusted for energy and fat intake.
‡Additionally adjusted for HDL cholesterol.

highest tertile had HDL-C greater than 1.39 mmol/l. The frequency of the T allele carriers increased according to HDL-C tertiles within AMI group. The T allele carriers were found in 40% of the 53 men with lowest HDL-C, in 48% of the 45 men with middle value HDL-C, and in 60% of the 25 men with highest HDL-C tertile (χ^2 test, p = 0.094 for trend). However, this trend was not found in the control group (table 4).

The subgroup analysis (table 5) revealed a significant interaction between HL C-480T polymorphism and HDL-C tertiles (p = 0.002). Those men who had CC genotype and whose HDL-C concentration was in the lowest or in the second lowest tertile had a 4/1 (95% CI, 1.7 to 9.6; p = 0.002) and 3.3/1 (95% CI, 1.4 to 7.8; p = 0.008) risk of developing AMI, respectively, compared with those in the highest HDL-C tertile after adjusting for age, BMI, smoking, hypertension, diabetes, family history of coronary disease, total cholesterol, triglycerides, and energy and fat intake.

DISCUSSION

The present study examined the role of HL C-480T polymorphism and serum HDL-C on a nine year follow up risk of AMI in originally healthy middle aged men. In this prospective study, we found that men with CC genotype had a slightly higher risk of developing AMI than did T allele carriers. Moreover, in secondary data analysis we found a highly significant interaction between the HL C-480T polymorphism and HDL-C levels in predicting development of AMI. This interaction revealed that men with the CC genotype and whose HDL-C was in the lowest tertile

Table 4 Distribution of HL C-480T genotypes according to HDL-C tertile

	Lowest tertile		Middle tertile		Highest tertile		p Value
Group	CC	CT, TT	CC	CT, TT	CC	CT, TT	for trend
AMI	32 (60%)	21	25 (52%)	23	10 (40%)	15	0.094
Control	39 (52%)	36	35 (42.7%)	47	50 (48.5%)	53	0.722

Data are numbers of subjects (per cent).
AMI, acute myocardial infarction.

Table 5 Adjusted relative risk of acute myocardial infarction according to hepatic lipase C-480T genotype status and levels of HDL-C

HDL-C (mmol/l)	HL C-480T genotype		
	CC (n = 191)	CT, TT (n = 195)	All (n = 386)
Lowest tertile	3.992†	2.426	3.378*
95% CI	(1.656–9.627)	(0.923–6.381)	(1.779–6.412)
Middle tertile	3.264‡	2.219	2.748*
95% CI	(1.358–7.847)	(0.920–5.356)	(1.506–5.017)
Highest tertile	1.0	0.968	1.0
95% CI		(0.376–2.488)	

Relative risk is adjusted for age, body mass index, smoking, years of hypertension, diabetes, family history of coronary disease, total cholesterol, triglycerides, and energy and fat intake. Total model <0.001; p value for interaction, 0.002.
CI, confidence interval. *p<0.001; †p = 0.002; ‡ p = 0.008, difference from the highest HDL-C tertile.

(<1.14 mmol/l) appeared to have a higher risk of developing AMI than did other HDL-C and HL genotype combinations.

There is evidence for an interaction of HL C-480T polymorphism with dietary fat intake,[17] and with medications that lower lipids.[18] In our study, such medication was used by only one subject, and it therefore could not have had a significant effect on our results. Dietary saturated fatty acids and dietary cholesterol were similar in men in the AMI and the matched control groups, which diminished the possibility of diet affecting our study. We also added total energy and total fat intake as covariates in multivariate analysis, which did not make any notable change, suggesting that energy and fat intake had no major effect on our results.

The previous findings as to the relationship between HL C-480T polymorphism and CAD are inconsistent.[7 12–15] One possible reason for the mixed results may be the interaction between HL C-480T genotype and HDL-C levels on CAD. However, no earlier data are available on whether the relation between HL C-480T polymorphism and AMI risk is modified by HDL-C levels. Thus, our results may explain some earlier ambiguous results on the association between HL C-480T genotype and CAD, and can be interpreted in two different ways. First, they may suggest that the HL C-480T polymorphism affects AMI risk differently in men with different HDL-C levels; or secondly, that the atherogenicity of low concentrations of HDL-C maybe modulated diversely by different C-480T genotypes. This finding is not fully comparable with the findings of Liu *et al*,[11] who found a similar interaction between CETP TaqIB polymorphism and HDL levels in predicting first myocardial infarction. However, our results support the idea that assessing the effect of HDL-C on AMI risk may require taking additional factors, such as HL C-480T or CETP TaqIB polymorphisms, into account.

We do not have any plausible explanation for how C-480T polymorphism interacts with HDL-C levels in predicting the risk for AMI. However, the C-480T polymorphism is a key determinant of HL levels, accounting for up to 38% of HL level variability.[19] The T allele has been shown to decrease the transcriptional activity of the HL gene also in the laboratory.[9] Our findings may be related to the HL activity either in the liver or alternatively in artery wall macrophages.[4 20]

Since HL is expressed within the macrophages of atherosclerosis plaques,[4 20] it has been postulated that HL might have a direct role in the pathogenesis of atherosclerosis without changes in plasma lipoprotein metabolism.[4 20] In theory, C-480T polymorphism and HDL-C levels may have synergistic effects on HL expression either in the arterial wall macrophages and/or in the liver, which may lead to varying risk for atherosclerotic diseases, such as AMI, in different individuals. Men with CC genotype together with low HDL-C

may have higher HL activity. This could contribute to the production of a high risk lipid profile by reducing the HDL_2 cholesterol pool and increasing small, dense LDL particles in the plasma, leading to impaired reverse cholesterol transport.[21] In addition, high HL expression in arterial macrophages may lead to enhanced foam cell formation within atherosclerotic plaques and thus faster progression of atherosclerosis.[4 20] The latter idea is supported by the fact that two independent atherosusceptible mouse models have shown that the localised production and accumulation of HL by macrophages present in the vessel wall contribute significantly to aortic lesion formation.[20] On the other hand, men with the T allele together with high HDL-C may have lower HL activity, leading to a lower risk lipid profile,[21 22] more effective reverse cholesterol transport,[21] less foam cell formation, and thus slower progression of atherosclerosis.[20]

In summary, our findings suggest that HL CC genotype, previously associated with high HL activity,[7–9 12 14] together with a low HDL-C level, may increase the risk of developing AMI. Our study does not determine the effect of HL genotype on the risk of developing AMI alone, but our data suggest the possibility that genetic screening for HL C-480T polymorphism together with determining the serum HDL-C level maybe helpful in identifying persons at high risk for AMI. Nonetheless, more research is still needed to clarify the complex role of HDL-C and HL C-480T polymorphism in the development of CAD.

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